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Improvement of Disease-Specific Quality of Life and Dyspeptic Symptoms with Dlbs2411, A Bioactive Fraction of Cinnamomum Burmannii, in Patients with Functional Dyspepsia

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Abstract

Functional dyspepsia is a common disorder of gut–brain interaction that substantially impairs quality of life, while available pharmacological treatments provide modest benefits and may cause adverse effects during prolonged use. This study aimed to evaluate the effects, durability, and safety of DLBS2411, a standardized bioactive fraction of Cinnamomum burmannii, in adults with functional dyspepsia. This prospective multicenter study enrolled 53 adults with Rome IV-defined, Helicobacter pylori-negative functional dyspepsia from seven hospitals in Indonesia. Participants received DLBS2411 at a dose of 250 mg twice daily for 28 days and were followed for an additional eight weeks. Disease-specific quality of life was assessed using the Short-Form Nepean Dyspepsia Index (SF-NDI), while eight dyspeptic symptoms were evaluated using visual analog scales (VAS). Safety was assessed through adverse event monitoring, vital signs, electrocardiography, and laboratory examinations. The mean SF-NDI score improved by 53% at Week 4 and 67% at Week 12. All eight dyspeptic symptoms showed significant improvement, and the proportion of participants reporting adequate relief increased from 55% at Week 2 to 76% at Week 12. DLBS2411 was generally well tolerated, with no treatment-related serious adverse events reported. In conclusion, DLBS2411 was associated with early and sustained improvements in disease-specific quality of life and dyspeptic symptoms; however, placebo-controlled trials are required to confirm its efficacy and clinical therapeutic value.

INTRODUCTION

Functional dyspepsia (FD) is one of the most common disorders of gut–brain interaction encountered in clinical practice. A meta-analysis of 44 population-based studies involving 256,915 participants from 40 countries estimated a global pooled prevalence of 8.4%, with a prevalence of 6.8% when the restrictive Rome IV criteria were applied and a consistently

higher burden among women and populations in developing economies (Lee et al., 2024). The Rome Foundation global epidemiology study, which surveyed 54,127 adults across 26 countries, reported a Rome IV FD prevalence of 7.2%, predominantly affecting women and younger adults and being associated with psychological distress, impaired quality of life, and increased healthcare utilization. Postprandial distress syndrome (PDS) accounted for approximately two-thirds of cases, epigastric pain syndrome (EPS) accounted for 15%, and overlapping PDS–EPS accounted for the remaining cases.(Sperber et al., 2021; Tack et al., 2025), In Indonesia, dyspepsia is among the ten most frequent diagnoses in both inpatient and outpatient care, and a regional multicenter survey found that 43% of patients presenting with uninvestigated dyspepsia ultimately met the criteria for FD, indicating a substantial burden in primary care.(Syam et al., 2023)

The pathophysiological understanding of FD has shifted over the past decade from a predominantly motility- and perception-based model toward one in which the duodenum plays a central role. Impaired duodenal mucosal integrity (Ronkainen et al., 2021), low-grade eosinophilic and mast cell infiltration, epithelial barrier dysfunction with increased permeability, and altered duodenal microbial communities have been demonstrated in patients with FD and linked to symptom generation through neuroimmune signaling. (Wauters et al., 2022) Postinfectious onset following acute gastroenteritis is now recognized as a distinct phenotype, and duodenal acid exposure remains a plausible upstream trigger for mucosal injury, providing a mechanistic rationale for acid-modifying therapy even in the absence of endoscopic abnormalities.(Zhang et al., 2024)

Despite these advances, current pharmacological management of FD remains suboptimal (Bosman et al., 2023). A network meta-analysis of 71 randomized trials involving 19,243 participants found that tricyclic antidepressants, histamine-2 receptor antagonists, proton pump inhibitors (PPIs), prokinetics, and acotiamide were more effective than placebo; however, effect sizes were modest, no treatment (Jones et al., 2023) demonstrated clear superiority, and adverse events limited the use of some effective therapies. (Ford et al., 2021) Current guidelines therefore recommend a stepwise empirical treatment strategy beginning with acid suppression.(Adam & Berzonsky, 2006),(Wauters et al., 2021) At the same time, concerns regarding the consequences of prolonged and often inappropriate acid suppression have increased considerably. Global PPI utilization continues to rise, with a substantial proportion of prescriptions lacking appropriate indications, and long-term exposure has been associated with enteric infections, micronutrient malabsorption, rebound acid hypersecretion after withdrawal, and other potential adverse outcomes.(Shanika et al., 2023) The balance between patients' expectations of pharmacological benefit and reassurance, and the recommendation against indefinite use of certain therapeutic classes, represents an important clinical challenge.

Given these considerations, complementary and plant-derived therapies have continued to receive substantial attention. A meta-analysis of 49 randomized trials involving 6,987 patients showed that herbal preparations improved FD symptoms compared with placebo (standardized mean difference −0.58; 95% CI −0.66 to −0.51) without increasing adverse events (Huang et al., 2021).(Heiran et al., 2022) Individual well-designed trials of standardized botanical preparations have also reported therapeutic benefits. (N-Y et al., 2023),(Samimi et

al., 2024) However, limitations in much of this literature include poorly characterized products and inconsistent standardization, which hinder reproducibility and regulatory acceptance.

Cinnamomum burmannii (Nees & T. Nees) Blume, commonly known as Indonesian cinnamon and locally referred to as kayu manis, has a long history of ethnomedical use for nausea, flatulence, and epigastric discomfort, supported by extensive phytochemical and pharmacological research. (Tjandrawinata et al., 2013) DLBS2411 is a bioactive fraction derived from the cortex of the species through a proprietary and validated aqueous extraction and liquid–liquid fractionation process, standardized to A-type proanthocyanidin trimer (cinnamtannin B1). (Tjandrawinata et al., 2013), (Wulandari et al., 2016)Unlike many botanical preparations investigated for FD, DLBS2411 has a defined dual mechanism of action. It downregulates gastric H^+/K^+-ATPase gene expression and competitively inhibits enzyme activity in gastric parietal cells and HEK293 cells, with increased potency under lower pH conditions. It also enhances mucosal defense by inducing IKKα phosphorylation and NF-κB activation, thereby upregulating cyclooxygenase-2 (COX-2), suppressing 15-hydroxyprostaglandin dehydrogenase, increasing prostaglandin E2 (PGE2) and MUC5AC expression, and stimulating nitric oxide production. A subsequent network pharmacology and molecular docking analysis identified consistent molecular targets, including PTGS1, PTGS2, HPGD, NOS2, and ATP4A, supporting a proton pump-modulating and mucoprotective mechanism attributable to the bioactive fraction as a whole rather than a single compound.(Rustan et al., 2024)

These mechanisms have demonstrated biological activity in preclinical and clinical studies. DLBS2411 reduced ulcer area and ulcerative lesion indices in ethanol-, indomethacin-, and acetic acid-induced gastric ulcer models in Wistar rats, (Rustan et al., 2024) while acute, 90-day subchronic, and teratogenicity studies demonstrated a wide safety margin. In a three-arm, double-blind, placebo-controlled study involving 54 healthy volunteers, single doses of DLBS2411 (250 mg and 500 mg) increased the 24-hour mean intragastric pH compared with placebo, significantly reduced the time required to achieve pH > 4 (129.9 ± 128.2 and 92.9 ± 106.8 minutes versus 196.9 ± 99.7 minutes), and were well tolerated. The effect was most pronounced during the first 12 hours after administration, providing the rationale for twice-daily dosing.(Tjandrawinata et al., 2025)

Whether this pharmacodynamic profile translated into symptomatic improvement and enhanced quality of life in patients with FD had not previously been evaluated. Therefore, this multicenter trial investigated DLBS2411 administered at 250 mg twice daily for four weeks in adults with Rome IV-defined FD, followed by an additional eight-week observational period after treatment completion. This publication reports outcomes observed in the DLBS2411 treatment arm and characterizes the magnitude, time course, durability of response, and safety profile of the investigational product.

METHOD

Study design and ethics

This prospective study was conducted from 22 December 2022 to 1 October 2025 at seven centers in Indonesia: Dr. Cipto Mangunkusumo National General Hospital, Fatmawati General Hospital, Budhi Asih Hospital, Pasar Rebo Hospital (Jakarta), Dr. Kariadi General Hospital (Semarang), and Dr. Moewardi Hospital and Universitas Sebelas Maret Hospital

(Surakarta). Participants received DLBS2411 at a dose of 250 mg twice daily for 28 days and were followed for an additional eight weeks after treatment completion. Efficacy assessments were performed at baseline and Weeks 2, 4, and 12, while laboratory safety parameters were evaluated at baseline and Week 4. Vital signs and adverse events were monitored throughout the 12-week study period. The trial was conducted in accordance with the Declaration of Helsinki, ICH E6(R2) Good Clinical Practice guidelines, and Indonesian National Agency of Drug and Food Control (NADFC/BPOM) Regulation No. 8/2024. The study protocol, amendments, and informed consent documents were approved by the independent ethics committees of participating institutions; institutions without their own ethics committees adopted approval from Dr. Cipto Mangunkusumo Hospital. Written informed consent was obtained from all participants before any trial-related procedures were conducted.

Participants

Eligible participants were men and women aged 18–75 years who fulfilled Rome IV criteria for FD, that is, one or more of bothersome postprandial fullness, early satiation preventing completion of a regular meal, epigastric pain or epigastric burning, present for at least three months with symptom onset at least six months before screening, in the absence of structural disease capable of explaining the symptoms as verified by a normal esophagogastroduodenoscopy performed within the previous three years. Where no endoscopic record within that window existed, upper endoscopy was performed before enrolment. Both EPS and PDS subtypes were eligible, since most patients with FD exhibit features of both. All participants were required to test negative for H. pylori by urea breath test, histology or rapid urease test during screening, to be able to take oral medication, and to be able and willing to complete a participant diary.

Key exclusion criteria were pregnancy, breastfeeding or intention to conceive; clinically suspected COVID-19; gastro-esophageal reflux disease documented endoscopically or by predominant heartburn or acid regurgitation two or more times weekly in the preceding year; known or suspected Zollinger–Ellison syndrome; gastrointestinal malignancy or malignancy-associated ulceration; hepatic cirrhosis or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than three times the upper limit of normal; hemodialysis or estimated glomerular filtration rate (eGFR) below 60 mL/min; New York Heart Association class III–IV heart failure or other uncontrolled chronic disease including blood pressure ≥ 160/100 mmHg or HbA1c ≥ 7%; serious intercurrent infection or illness judged to interfere with safety or evaluation; use within two weeks of screening of any drug affecting the upper gastrointestinal tract, including prokinetics, histamine-2 receptor antagonists, PPIs, potassium-competitive acid blockers, sucralfate, rebamipide or gastric-relevant herbal medicines; and participation in another clinical study within 30 days.

The exclusion of H. pylori-positive individuals was prespecified because infection influences both the natural history of FD and the response to antibiotic therapy, and eradication itself improves symptoms in a proportion of patients; its inclusion would have introduced an uncontrolled confounder. Indonesia has an unusually low national prevalence of H. pylori infection relative to neighboring Asian countries,26 so this restriction excluded comparatively few otherwise eligible candidates. Uncontrolled diabetes was excluded to avoid conflating FD with diabetic gastroparesis, and uncontrolled cardiovascular disease to avoid the overlapping symptomatology and polypharmacy that accompany it.

Treatment

Eligible participants were treated with DLBS2411 (Redacid®, PT Dexa Medica, Indonesia) caplet 250 mg twice daily, at least 30 minutes before the morning and evening meals, for 28 consecutive days. Study product was stored at 8–30 °C protected from humidity, with daily temperature logging. Antacid chewing tablets (Dexanta®, PT Dexa Medica) were dispensed with the study product as escape therapy, to be taken only for intolerable dyspeptic symptoms requiring immediate relief. Packs of ten tablets were supplied; consumption beyond ten tablets required consultation with the site principal investigator, who determined whether continued participation was appropriate and documented the justification for any additional supply. Antacid was permitted on the basis that its efficacy in FD has not been shown to exceed that of placebo, and restricting escape medication to a single sponsor-supplied product minimized inter-participant variability. Prokinetics, acid-release inhibitors, gastric mucosal protectors and gastric-relevant herbal preparations remained prohibited throughout the study, as did regular chronic use of non-steroidal anti-inflammatory drugs, systemic glucocorticosteroids, aspirin above 100 mg daily, cholinergics, anticholinergics and spasmolytics. Adherence was assessed by caplet count at each visit against the participant diary.

Efficacy endpoints and assessments

The primary efficacy endpoint was the improvement in disease-specific quality of life, measured as the mean reduction from baseline in the total Short-Form Nepean Dyspepsia Index (SF-NDI) after four weeks of therapy. Secondary endpoints were the mean reduction in total SF-NDI at Week 2 and at Week 12 (eight weeks after the end of therapy); the change in intensity of eight individual dyspeptic symptoms measured on a visual analogue scale (VAS) at Week 2, 4 and 12; the proportion of participants reporting adequate or satisfactory relief of FD symptoms on their own overall assessment at each timepoint; and the number of escape antacid tablets consumed during the four weeks of therapy. Prespecified exploratory endpoints were the interval in days from the last day of treatment to the first day of escape therapy use, and the number of participants using escape therapy during the eight-week observational period.

The Nepean Dyspepsia Index was developed as a disease-specific quality-of-life instrument and subsequently condensed to a ten-item short form covering five domains — tension, interference with daily activities, eating and drinking, knowledge and control, and work or study — each rated on a five-point Likert scale from 0 to 4, giving a total score of 0 to 40 with higher scores denoting poorer quality of life.(Miftahussurur et al., 2021) The short form demonstrates adequate internal consistency, correlates closely with the original instrument and is highly responsive to change, and the Indonesian-language version used here has been separately translated and validated.[,] It was administered by the investigator through a face-to-face interview at baseline and at weeks 2, 4 and 12.

Symptom intensity was recorded on a 100-mm VAS anchored at "no pain" and "the worst pain as it could possibly be", scored by measuring the distance from the left anchor. Eight symptoms were assessed with operational definitions supplied to participants: postprandial fullness, early satiety, bloating, epigastric discomfort, epigastric pain, postprandial nausea, excessive belching after meals, and vomiting. The VAS is sensitive to change and is widely used as an outcome measure in FD trials.

Safety assessments

Safety was evaluated in all participants who received at least one dose of study product. Vital signs (body temperature, blood pressure, heart rate and respiratory rate) and adverse events were assessed at baseline and at every follow-up visit including Week 12. Twelve-lead electrocardiography, liver function (ALT and AST) and renal function (serum creatinine and eGFR) were measured at baseline and at Week 4. Adverse events were recorded by participants in a diary and presented descriptively by system organ class, with the investigator assigning severity, causal relationship, action taken, treatment given and outcome for each event.

Statistical analysis

The full analysis set followed the intention-to-treat (ITT) principle and comprised all randomized participants who received at least one dose of study product and returned for at least one post-baseline visit with evaluable efficacy data. Continuous variables are summarized as mean ± standard deviation and categorical variables as counts and percentages. Changes from baseline over time in SF-NDI and VAS scores were analyzed by repeated-measures analysis of variance followed by post-hoc paired t-tests comparing each post-baseline timepoint with baseline; p values for secondary endpoints were adjusted for multiplicity using the Holm procedure, while exploratory endpoints were analyzed without such adjustment. Mean changes from baseline are presented with two-sided 95% confidence intervals. Where distributional assumptions were not met, variables were log-transformed or the corresponding non-parametric test was applied. Missing values in within-group repeated-measures analyses were imputed by prespecified summary-based methods. All tests were two-sided at the 5% significance level. Analyses were performed in RStudio version 2025.09.0+387 (Posit PBC, Boston, MA, USA).

RESULTS AND DISCUSSION

Participant disposition and baseline characteristics

Fifty-three eligible participants were allocated to receive the investigated treatment with DLBS2411. Fifty-one participants (96%) completed the full 12-week study. Two discontinued: one was withdrawn by the investigator after taking three tablets of ranitidine during the first fortnight of the intervention, and one withdrew at their own request on the third day of treatment because of a perceived rise in blood pressure. Evaluable efficacy data were available for 53 participants at baseline and Week 2, 51 at Week 4 and 49 at week 12. Three participants met criteria for major protocol deviation — one began treatment after only 11 of the required 14 washout days for prokinetic therapy, and two took fewer than 80% of prescribed doses — leaving 48 participants in the per-protocol set.

Baseline characteristics are shown in Table 1. The cohort was predominantly female (37 of 53, 70%) with a median age of 41 years (interquartile range 30–49). Ninety-one per cent had never smoked, none reported current or previous regular alcohol consumption, and the mean body mass index was 23.62 ± 4.86 kg/m², in the upper normal range. Forty-three participants (81%) had an established diagnosis of FD before enrolment while ten (19%) were newly diagnosed during screening. Comorbidity was uncommon; hypertension, present in ten participants (19%), was the most frequent, and three (6%) had a documented psychiatric disorder, in each case anxiety.

Baseline disease severity and safety parameters are summarized in Table 2. The mean total SF-NDI score was 16.02 ± 7.92 out of a possible 40. Individual symptom intensities clustered in the 36–51 mm range on the 100-mm VAS — bloating 50.66 ± 28.74 mm, epigastric discomfort 50.45 ± 30.24 mm and postprandial fullness 48.62 ± 28.15 mm being the most intense — with the conspicuous exception of vomiting at 19.66 ± 26.18 mm, consistent with the Rome IV observation that vomiting is unusual in FD.

Exposure, adherence and concomitant medication

All 53 participants received at least one dose. Median exposure was 30 days (range 5–33; mean 29.58 ± 4.01), consistent with the intended 28-day course. Adherence was good (≥ 80% of prescribed doses) in 49 participants (92%), with a mean of 97% ± 16% in the ITT set. Fifteen participants (28%) used at least one concomitant medication; amlodipine was the most frequent, mirroring the prevalence of hypertension at baseline, followed by antidepressant and anxiolytic agents in the small number of participants with documented psychiatric comorbidity, both of which were permitted by protocol. Only two participants took a medication with the potential to interfere with evaluation — the ranitidine described above, which led to withdrawal, and a five-day course of levofloxacin.

Primary efficacy endpoint

Total SF-NDI improved substantially and progressively throughout the study (Table 3, Figure 1). The mean score fell from 16.02 ± 7.92 at baseline to 7.59 ± 7.49 at Week 4, a mean reduction of 8.60 points (95% CI −10.81 to −6.40; $p < 0.001$), corresponding to a 53% improvement in disease-specific quality of life over four weeks of therapy.

Secondary efficacy endpoints

Improvement in quality of life was already evident after two weeks, the total SF-NDI having fallen to 9.89 ± 8.25 (mean change −6.21; 95% CI −8.64 to −3.77; $p < 0.001$), that is, approximately 39% improvement within the first fortnight. Notably, the gain was not only maintained but extended during the eight weeks after treatment ended: at week 12 the mean score was 5.24 ± 6.02, a reduction of 10.79 points (67%) from baseline (95% CI −13.11 to −8.46; $p < 0.001$).

All eight individual symptoms improved significantly from baseline at every assessment (Table 3). At the end of therapy the largest absolute reductions were seen for epigastric discomfort (−28.50 mm; 95% CI −38.42 to −18.59), postprandial fullness (−27.94 mm; −40.04 to −15.84) and epigastric pain (−26.96 mm; −36.26 to −17.66), while the smallest was for vomiting (−10.77 mm; −15.89 to −5.65), the symptom with the lowest baseline intensity. Expressed proportionally, week-4 reductions ranged from 43% for early satiety to 55% for epigastric pain. As with the quality-of-life score, symptom intensity continued to decline through the observational phase; by Week 12, mean VAS scores for every symptom had fallen below 20 mm, the range conventionally regarded as mild.

Self-reported adequate relief tracked these objective changes closely (Table 4). More than half of participants (29 of 53, 55%) considered themselves adequately relieved as early as Week 2; this proportion rose to 69% (35 of 51) at the end of therapy and to 76% (37 of 49) at Week 12.

Escape antacid was used by fewer than half of participants at any timepoint — 26 (49%) during the first two weeks, 25 (49%) during weeks 3–4 and 23 (46%) during the eight-week observational phase. Among users, median consumption was 3 tablets (interquartile range 1–

5) in the first fortnight and 4 tablets (2–7) in the second, that is, roughly one tablet every four to five days.

Exploratory endpoints

Among participants who required escape therapy after the end of treatment, the median interval from the last treatment day to the first antacid tablet was 5 days (interquartile range 0–12), and median total consumption across the entire eight-week observational period was 7 tablets (3–12) — a low rate of rescue medication use during a period in which no active study treatment was being taken.

Safety and tolerability

Thirty-one participants (58%) reported at least one adverse event during the 12-week study period. Gastrointestinal disorders were the most frequent system organ class, affecting 20 participants (38%) — an expected finding in a cohort recruited for upper gastrointestinal symptoms — with diarrhea (11%), abdominal pain (9%), stomachache (8%), nausea (6%) and heartburn (6%) the commonest preferred terms. Nervous system disorders were reported by 10 participants (19%), almost entirely dizziness (17%); respiratory, thoracic and mediastinal disorders by 12 (23%), principally influenza-like illness and cough; and general disorders by 10 (19%). Events were mild in 18 participants (34%) and moderate in 23 (43%); eight participants (15%) experienced an event graded severe. Causality assessment by the investigators attributed a single event — one case of diarrhea, on the basis of its onset during the treatment period — as possibly related to the investigational product; all other events were judged unrelated. One participant permanently discontinued study medication for perceived blood-pressure elevation. Most events required no change to study treatment, 30 participants (57%) had recovered by the end of follow-up and three (6%) were stable at last assessment. Two serious adverse events occurred, both requiring hospitalization and neither considered treatment-related: one participant with chest pain and palpitations was diagnosed with angina, treated and discharged in stable condition; and one participant with a documented pre-enrolment history of anxiety experienced worsening anxiety requiring psychiatric admission, was subsequently diagnosed with a major affective disorder, and was discharged after stabilization with continued outpatient follow-up. No deaths occurred.

Objective safety parameters were unremarkable (Table 5). Body temperature, blood pressure, heart rate and respiratory rate were stable across all four assessments.

In this cohort of 53 adults with Rome IV-defined, H. pylori-negative functional dyspepsia, four weeks of DLBS2411 250 mg twice daily was accompanied by a 53% reduction in the total SF-NDI score and by statistically significant improvement in all eight individual dyspeptic symptoms at every assessment. Three features of the response merit emphasis. First, it was early: nearly three-quarters of the four-week quality-of-life gain and more than half of the symptom relief had accrued by Week 2, and 55% of participants already regarded themselves as adequately relieved at that point. Second, it was uniform across the symptom spectrum, encompassing both the meal-related symptoms characteristic of PDS and the pain-predominant symptoms of EPS, rather than being confined to one domain. Third, and least expected, the improvement was not merely maintained after treatment stopped but deepened: total SF-NDI fell a further 3.2 points during the 8 weeks off treatment, and every symptom score continued to decline, while fewer than half of participants used any escape antacid during that period.

Coherence with the pharmacology of DLBS2411

The breadth and consistency of the response are congruent with the dual mechanism established for this fraction. Acid suppression through down-regulation of H^+/K^+ ATPase gene expression and competitive inhibition of the enzyme[21] provides a plausible route to relief of epigastric pain and burning, the symptoms most consistently responsive to acid suppression in FD trials.[13] The cytoprotective arm — COX-2 induction with 15-PGDH suppression, increased PGE_2 and MUC5AC expression, and nitric oxide-mediated enhancement of mucosal blood flow[22,23] — is of particular interest given the current emphasis on impaired duodenal mucosal integrity, low-grade immune activation and increased permeability as generators of FD symptoms.[5–7] A preparation that both reduces the acid load reaching the duodenum and strengthens mucus, bicarbonate and microcirculatory defense addresses two ends of the same pathophysiological sequence, which may account for the improvement observed across meal-related as well as pain-predominant symptoms. That interpretation remains mechanistic inference: no mucosal, permeability or histological endpoints were collected in this trial.

The observed dose regimen also follows directly from earlier pharmacodynamic work. In healthy volunteers a single dose raised intragastric pH predominantly during the 12 hours after administration, with little effect overnight, which prompted the twice-daily schedule used here.[25] The absence of an apparent dose–response between 250 mg and 500 mg in that study supported selection of the lower dose, and the present tolerability data give no reason to revisit that choice.

Interpretation in the context of the placebo response in functional dyspepsia

The central interpretive caution is that these are within-arm data. The placebo response in FD is among the largest in gastroenterology: pooled estimates range from 32% to 44% depending on responder definition, and are higher still when improvement rather than complete relief is the criterion.[29,30] Lower baseline symptom severity, longer trial duration, non-smoking status and higher body mass index have all been identified as predictors of a larger placebo response.[30,31] Consequently, the magnitude of change reported here should be read as the total response observed on treatment — pharmacological effect, contextual and expectancy effects, regression to the mean and the natural or spontaneous remitting course of a relapsing disorder combined — and not as an absolute estimate of drug effect. The randomized comparison against placebo-control is what will determine whether the pharmacological contribution is material.

Two features of the present data are nevertheless difficult to attribute wholly to non-specific effects and warrant scrutiny in the controlled analysis. The continued improvement over eight weeks after treatment withdrawal runs counter to the usual decay of placebo response over time,[31] and the low rate of escape antacid use during that un-medicated period argues against symptomatic deterioration being masked by rescue therapy. Whether this reflects mucosal healing that outlasts drug exposure, the natural history of FD, or the extended contact and reassurance inherent in trial participation cannot be resolved with the present analysis.

Comparison with other therapeutic options

Set against the wider evidence (Nojkov et al., 2020) base, the improvement recorded here is at least comparable to what is achieved with established agents. The largest network meta-analysis in FD found that although tricyclic antidepressants, acid suppressants and prokinetics

all outperform placebo, the therapeutic gain over placebo is modest for every class, no drug is clearly superior, and the most effective agents carry the greatest burden of adverse effects.[13] Herbal preparations occupy a defensible position in this landscape: a meta-analysis of 49 trials found a standardized mean difference of −0.58 in favour of herbal treatment over placebo with no excess of adverse events,[17] and randomized trials of individual botanical preparations continue to report benefit.[18,19] What distinguishes DLBS2411 within that heterogeneous group is the degree of pharmaceutical and mechanistic characterization: a manufacturing process validated under Good Manufacturing Practice, standardization to a defined marker (A-type proanthocyanidin trimer), with molecular targets identified in vitro and corroborated by network pharmacology, and demonstrated pharmacodynamic activity in humans.[21–25] Poor product characterization has been the principal obstacle to acceptance of botanical therapies in FD, and it is largely absent here.

Clinical implications

The therapeutic dilemma in FD is well recognized. Guidelines recommend empirical acid suppression as first-line therapy,[14,15] yet FD is a chronic relapsing condition and prolonged PPI exposure is increasingly discouraged: global utilization continues to rise, a large share of prescriptions lacks a durable indication, and long-term use has been linked to enteric infection, micronutrient malabsorption and rebound hypersecretion on withdrawal.[16] Withholding pharmacotherapy is rarely an acceptable alternative in practice, since patients with normal endoscopic findings frequently interpret the absence of a prescription as the absence of care, with adverse consequences for psychological wellbeing and symptom experience. A well-characterized, well-tolerated, plant-derived preparation with a proton-pump-modulating and mucoprotective mechanism could occupy this space — as an option for patients who prefer a natural product, as maintenance or step-down therapy after an initial PPI course, or as first-line treatment in mild disease.

Strengths and limitations

The strengths of this work include the multicentre design spanning seven Indonesian hospitals across two provinces, which supports generalisability within the target population; strict Rome IV diagnostic criteria with mandatory endoscopic exclusion of structural disease; universal exclusion of H. pylori-positive individuals, removing a major confounder that is often left uncontrolled; a validated, locally translated disease-specific quality-of-life instrument as the primary endpoint rather than an unvalidated symptom score; high treatment adherence (mean 97%) and low attrition (4%); a prospectively defined statistical plan with multiplicity adjustment for secondary endpoints; a per-protocol sensitivity analysis showing concordant results; and an eight-week off-treatment follow-up, which is longer than that of most FD trials and permits assessment of durability.

The limitations are substantial and must temper interpretation. First and most importantly, this report presents a single arm therapy; without the placebo comparison the pharmacological effect of DLBS2411 cannot be quantified, and given the size of the placebo response in FD this is not a minor reservation. Second, the sample of 53 provides limited precision for uncommon adverse events and no capacity for reliable subgroup analysis by FD subtype, symptom severity or psychological comorbidity — analyses that would be informative given that PDS and EPS may respond differently to acid modification. Third, the four-week

treatment period does not address the maintenance or repeated-course use that a chronic relapsing disorder would require in practice, and no data beyond Week 12 were collected.

Future directions

Beyond the placebo-controlled analysis, an active-controlled trial against standard-dose PPI, with a non-inferiority design and a longer treatment period, would establish the product's place in the therapeutic sequence. Finally, incorporation of mechanistic endpoints — 24-hour intragastric pH monitoring, duodenal permeability measurement or mucosal eosinophil and mast-cell counts — into a future trial would connect the well-defined preclinical pharmacology to the clinical response with far greater confidence than is possible from symptom scores alone.

CONCLUSION

Four weeks of DLBS2411 administered at 250 mg twice daily were associated with clinically meaningful improvements in disease-specific quality of life and dyspeptic symptoms among adults with Rome IV-defined, Helicobacter pylori-negative functional dyspepsia. The total Short-Form Nepean (Arinton et al., 2006) Dyspepsia Index score decreased by 53% at Week 4 and by 67% at Week 12, while all eight assessed symptoms showed significant improvement. Adequate symptom relief was reported by 69% of participants at the end of treatment and by 76% at Week 12, indicating that improvements persisted and continued throughout the eight-week post-treatment follow-up period. DLBS2411 was generally well tolerated, with stable vital signs and no treatment-related serious adverse events reported. Nevertheless, because this analysis was based on a single-arm study design, the observed improvements could not be attributed solely to DLBS2411 without considering potential influences from placebo effects, regression to the mean, and the natural course of functional dyspepsia.

Future research should involve larger randomized, double-blind, placebo-controlled trials to establish the efficacy and safety of DLBS2411 more conclusively. Active-controlled noninferiority trials comparing DLBS2411 with standard-dose proton pump inhibitors are also recommended to clarify its potential role as an initial, maintenance, or step-down therapy. Longer treatment and follow-up periods are needed to evaluate sustained effectiveness, symptom recurrence, repeated treatment courses, and uncommon adverse events. Future studies should also examine treatment responses according to functional dyspepsia subtypes, baseline symptom severity, and psychological comorbidities. Incorporating mechanistic assessments, such as 24-hour intragastric pH monitoring, duodenal permeability measurements, and mucosal eosinophil and mast cell assessments, would further clarify whether clinical improvements are mediated by the proposed acid-modulating and mucoprotective mechanisms of DLBS2411.

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